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Trends of Survival in Neuroblastoma and Independent Risk Factors for Survival at a Single Institution

Tomohiro Saito, MD,[1] Yukiko Tsunematsu, MD,[2] Morihiro Saeki, MD,[3] Toshiro Honna, MD,[3] Eiichi Masaki, MD,[4] Yoko Kojima, MD[5] and Jun Miyauchi, MD[5]

To assess the progress of survival in neuroblastoma which varies with many risk factors and to evaluate the influence of these factors on survival as independent risk factors.

The study subjects were 159 neuroblastoma patients seen from 1965–1994 at the oldest and largest children's hospital in Japan. Trends of survival in three treatment eras—1965–81, 1982–86, 1987–94—were assessed by the Kaplan-Meier method for different sex, age at diagnosis, the clinical stage, the site of onset, and the histological type. Then the influence on survival of these factors as independent prognostic variables was evaluated by the Cox proportional hazards regression analysis.

Age at diagnosis, the clinical stage, the site of onset, the histological type, and the treatment era were independent risk factors in the order of their influence on survival. Unfavorable survival outcomes were obtained for patients with age at diagnosis above 1 year, the clinical stage of VI by the Evans classification, adrenal onset, and neuroblastoma rather than ganglioneuroblastoma. Survival improved from the first to the second and from the second to the third treatment era.

Improvement of survival in neuroblastoma took place during the past 3 decades. Age at diagnosis, the clinical stage, and the histological type have still remained overwhelming prognostic factors over the progress in treatment. Med. Pediatr. Oncol. 29:197–205, 1997.

Key words: neuroblastoma; survival rate; risk factors; age factors

INTRODUCTION

The overall survival of children with neoplasms has improved considerably during the past three decades [1,2,3,4]. But the improvement is largely attributable to the marked improvement in leukemias [1,2,3,4] and malignant lymphomas [1,2,3,4] which constitute the majority in childhood neoplasms. The improvement of survival in solid tumors has not been so remarkable [1,2,3,4,5]. This has been so in neuroblastoma, particularly in advanced stages [6,7]. However, at some institutions, a progress in survival has been claimed recently [8,9,10].

The prognosis of neuroblastoma varies considerably with many factors: sex, age at diagnosis, the clinical stage, the primary site, the histopathological subtype, and the treatment protocol [11]. Recently added to these are the method of identifying patients—by mass screening [12] —, karyotypic patterns, and amplification of oncogenes [13,14]. These prognostic factors are closely interrelated. Therefore, the appraisal of such factors requires an analysis accounting for possible confounding effects by such factors. There have been some studies in which independent risk factors were evaluated by multivariate analysis [15,16,17,18]. However, in few studies these factors were assessed in relation to the chronological advancement in treatment [9].

In this report the magnitude of contribution to improved prognosis by these factors were assessed by multivariate analysis incorporating secular trends of survival in the past three decades at a single institution. This study features inclusion of recent cases after 1990.

MATERIALS AND METHODS

All the patients diagnosed as having malignant neoplasms at the National Children's Hospital from 1965–1994 were registered. The registration was retrospective for the patients before 1990 and prospective after 1990. The registered data included the histology of the tumor tissues obtained at biopsy, surgery, or/and autopsy, which was reported from the pathology section with the SNOMED code [19]. From this registry all the patients of neuroblastoma or ganglioneuroblastoma were extracted for this study: the former consisted of 132 cases and the

[1]Division of Environmental Epidemiology at the National Children's Medical Research Center; [2]Department of Hematology, [3]Department of Surgery, [4]Department of Radiology and [5]Department of Pathology at the National Children's Hospital.

*Correspondence to: Dr. Tomohiro Saito, Environmental Epidemiology, National Children's Medical Research Center, 3–35–31 Taishido, Setagaya-ku, Tokyo, Japan 154.

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latter 33 cases. The diagnosis of these patients was established, in addition to the histology, by urinary catecholamine levels and imaging studies. Primary sites were determined from findings at diagnosis, surgery, and autopsy. Based on these clinical and laboratory findings, the patients were staged according to the Evans classification [20]. The information on the present status of these patients as of December, 1995 was obtained through a follow-up survey to each clinical department.

The patients were divided into the following three treatment eras in the analysis: 1965–1981, 1982–1986, and 1987–1994. The division was based on major changes in the treatment philosophy and strategies. Treatment in the first era consisted of surgical removal of the tumor followed by chemotherapy for unresected residual tumor including metastases. The chemotherapy mainly consisted of the combination of cyclophosphamide and vincristin; adriamycin was added, after its development, for advanced cases, mainly Stage III and IV patients. Treatment in the second era was featured by ''delayed primary operation'' for advanced cases. The surgical removal of the tumor was postponed until a sufficient reduction of the bulk of the primary tumor was attained—confirmed with the help of computed tomography—by a multi-agent chemotherapy in which cysplatin was added. Treatment in the third era was marked by four major changes in the strategy. A multi-agent high-dose chemotherapy with etoposide was introduced for advanced (Stage III and IV) patients. The chemotherapy was combined with autologous bone marrow transplantation as a rescue regimen. The delayed primary operation was elaborated on the timing of the operation which aimed at complete resection of the tumor. Several indices indicating invasiveness of the tumor around the major arteries and vertebrae were developed, with the help of angiography, I^{131}-meta-iodobenzylguanidine scintigraphy, and computed axial tomography, to judge a possibility of complete resection. The operation was performed when the indices fell below certain values. Irradiation to the primary and metastatic sites was done during surgery in advanced patients.

The data were analyzed by PC-SAS [21]. Associations between risk factors were assessed by the chi-square test for significance. Survival was assessed by the Kaplan-Meier method [22] in the LIFETEST procedure in the PC-SAS and the significant test employed was the log-rank test. The survival time employed was the time from diagnosis to death related to the neoplasm, to the date of final observation in living patients, or to death unrelated to the neoplasm—there was one such patient who died of congenital heart disease—which was treated as a censored observation. In presenting survival curves, 4-years was selected as the time for the last observation. This is because few deaths occurred after this time and cases with longer observation times were not plentiful in the most recent treatment era. The Cox proportional hazards regression analysis [23] was performed by the PHREG procedure in the PC-SAS to assess independent effects of each risk variable on survival.

Among the 165 registered patients, the information necessary for survival analysis was lacking in 6 patients. In 4 patients survival information was lacking, and in 2 the date of death was unknown. Excluding these patients, 159 cases were used in the analysis.

Risk factors analyzed in this study were the treatment era, sex, age at diagnosis, site of onset and its side of right or left, the clinical stage, and the histological type. In assessing survival by these factors, some were regrouped. Reasons for regrouping are stated in the results section. Other potential prognostic factors such as gene amplification, DNA index, and serum laboratory results were not included in this analysis. The information on these factors was available only in recent patients.

RESULTS

Treatment Era

Survival of 159 patients for the three eras, namely 1965–1981, 1982–1986, and 1987–1994, is shown in Figure 1. The number of analyzed patients in the three eras was 94, 33, and 32 respectively. The 4-year survival was improved from 42.0% ± 5.1% (Standard error: SE) in the first treatment era to 60.6% ± 8.5% in the second era and further to 80.2% ± 7.3% in the third era. The difference in survival among the three eras was statistically significant ($p < 0.001$).

Sex

There were 77 male and 82 female patients. The 4-year survival rate for the whole study period was 55.0% ± 5.7% for male and 51.4% ± 5.6% for female patients, and the difference was not statistically significant ($p < 0.05$).

Age at Diagnosis

Survival by age at diagnosis is shown in Figure 2. Age at diagnosis was grouped into the following: less than 1 year of age, 1 or 2 years of age, and 3 years of age or more. The 4-year survival rate was best in the age group of less than 1 year, and worst in the age group of 3 years or more. The difference in survival among the three groups was statistically significant ($p < 0.001$). Since there was no significant difference between the two age groups above 1 year, the difference in survival was attributed to a good prognosis of age group of less than 1 year.

Improvement in survival by age group during the three treatment eras was assessed and the results are presented in Table 1. In all age groups survival improved, although a statistically significant difference among the three eras

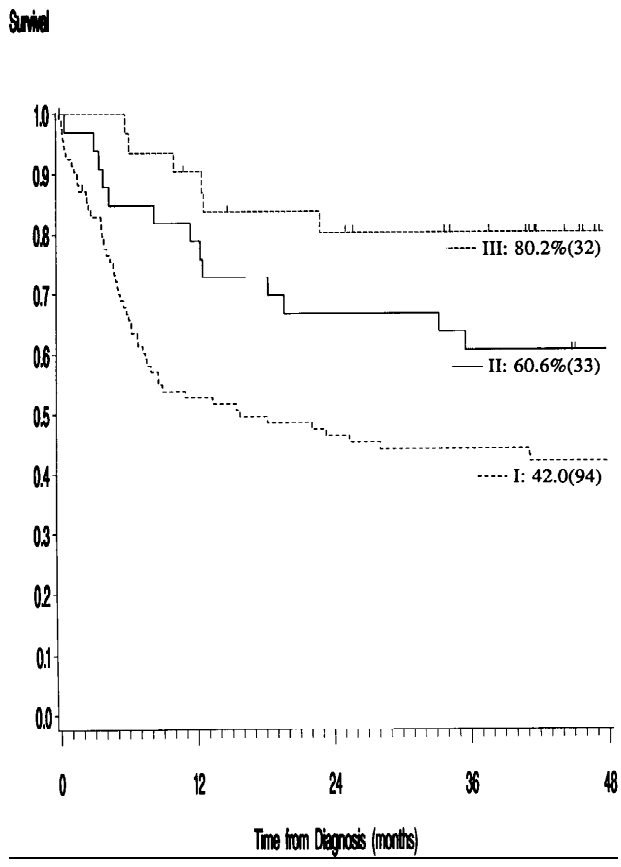

Fig. 1. Survival of Neuroblastoma Patients in the Three Treatment Eras. Treatment eras I: 1965–1981; II: 1982–1986; III: 1987–1994. The percentages are 4-year survival rates and the figures in parentheses are the numbers of analyzed cases. The short vertical lines indicate censored cases.

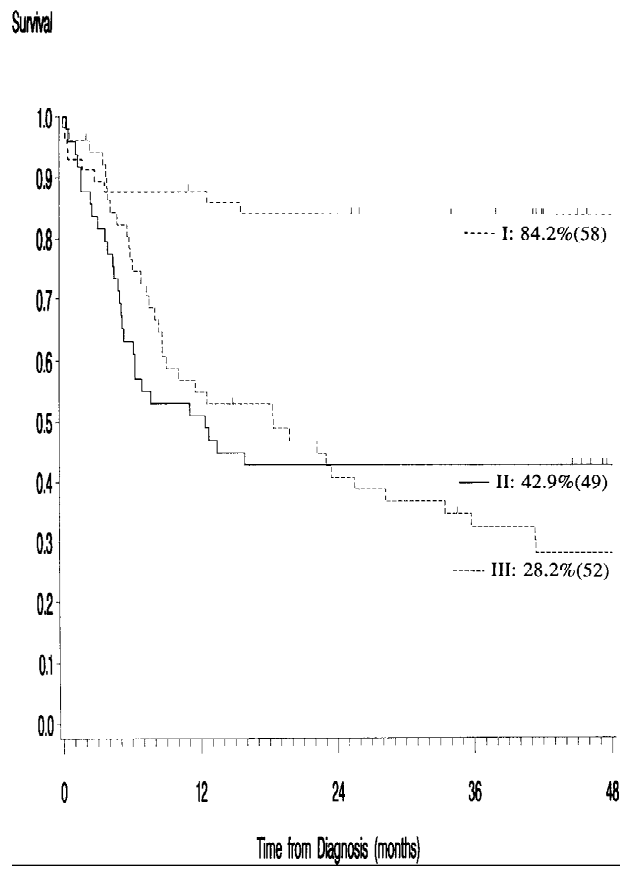

Fig. 2. Survival of Neuroblastoma Patients by Age at Diagnosis. Age at diagnosis I: less than 1 year; II: 1–2 years; III: 3 or more years. Four-year survival rates and the numbers of analyzed cases in parentheses are shown.

was obtained only in the eldest age group. In this group a significant improvement took place from the first to the second era, and no improvement was shown from the second to the third era. The improvement in the two young age groups may not have been great enough to show a statistically significant difference under a given sample size.

TABLE I. 4-year Survival Rate (%) by Age for the 3 Treatment Eras

Period		1965–81	1982–86	1987–94	Total	*P**
A	0	76.7 (30)	83.3 (12)	100 (16)	58	0.117
G	1–2	34.3 (35)	50.0 (6)	75.0 (8)	49	0.236
E	3<=	14.3 (29)	46.7 (15)	46.9 (8)	52	0.016

*: By the log rank test. Figures in parentheses and the total are the number of cases.

Clinical Stage

Survival by clinical stage is shown in Figure 3. The stage is that of Evans [20]. In 6 cases this information was not obtained and 153 cases were analyzed. Stage II, I, and IVs groups showed good prognosis, Stage III showed fair prognosis and Stage IV showed poor prognosis. The difference in survival among the five groups was statistically significant ($p < 0.001$).

Improvement in survival by clinical stage during the three eras is presented in Table II. In Stage IV, the improvement was statistically significant ($p < 0.05$) and this was due to the improvement from the second to the third era. None of the other groups showed a statistically significant improvement, even when the three eras were grouped into two by combining similar prognosis eras. This may be due to a small number in each era in each stratum of stage. However, it can be said that survival in patients with Stage I, II, III, and IVs became very good in the most recent era.

Site of Onset

Site of onset was variable from the neck to the sacrococcygeal region. Because of small numbers in some sites, the site of onset was grouped into three: neck or thorax; adrenal primaries; other abdominal and pelvic regions. The site of onset could not be identified in 3

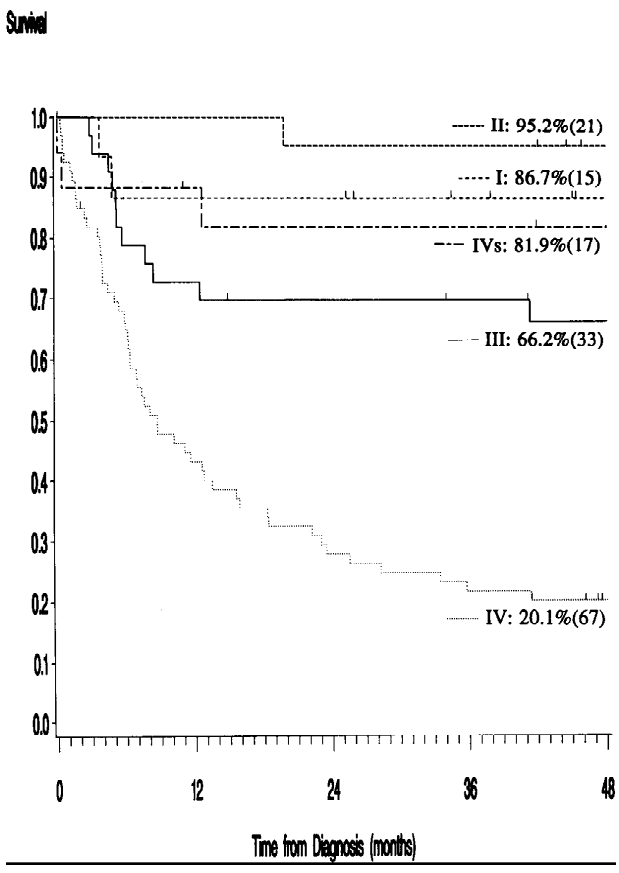

Fig. 3. Survival of Neuroblastoma Patients by Evans Stage. Evans stage: I, II, III, IV, and IV-S. Four-year survival rates and the numbers of analyzed cases in parentheses are shown.

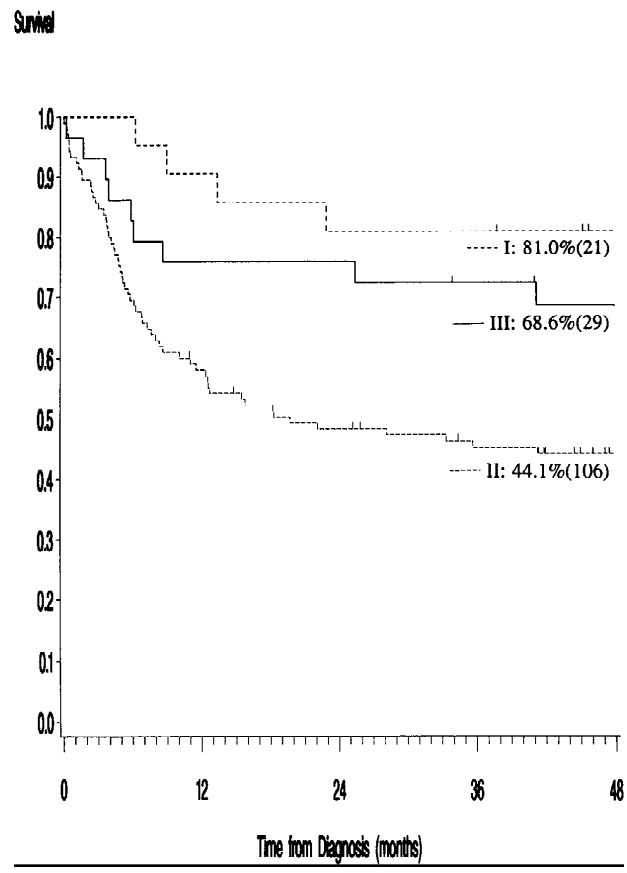

Fig. 4. Survival of Neuroblastoma Patients by Primary Site. Primary site I: Neck or thorax; II: Adrenal gland; III: Other abdominal or pelvic region. Four-year survival rates and the numbers of analyzed cases in parentheses are shown.

TABLE II. 4-year Survival Rate (%) by the Stage for the 3 Treatment Eras

Period		1965–81	1982–86	1987–94	Total	*P**
S	I	66.7 (6)	100 (5)	100 (4)	15	0.193
T	II	100 (7)	87.5 (8)	100 (6)	22	0.736
A	III	57.9 (19)	62.5 (8)	100 (5)	32	0.248
G	IV	11.7 (44)	11.1 (9)	53.9 (15)	67	0.021
E	IVs	81.8 (11)	66.7 (3)	100 (3)	17	0.663

*: By the log-rank test. Figures in parentheses are the number of cases.

TABLE III. 4-year Survival Rate (%) by the Site of Onset for the 3 Treatment Eras

Period		1965–81	1982–86	1987–94	Total	*P**
S I T E	Neck, thorax	70.0 (10)	100 (7)	75.0 (4)	21	0.194
	Abdominal	57.1 (21)	100 (3)	100 (5)	29	0.097
	Adrenal	33.3 (60)	43.5 (23)	76.8 (23)	106	0.006

*: By the log-rank test. Figures in parentheses and the total are the number of cases.

patients and these cases were excluded from this analysis for site of onset.

Survival by the three primary sites is shown in Figure 4. The difference in survival among the three site groups was statistically significant ($p < 0.001$). There was no statistically significant difference ($p > 0.05$) in survival between the two groups with fair prognosis, and the difference among the three groups was ascribed to the poor prognosis in patients with adrenal primaries.

Improvement in survival by site of onset is shown in Table III. Adrenal primaries showed a statistically significant improvement ($p < 0.01$). No statistically significant improvement was shown in the other sites ($p > 0.05$), even when two of the three eras were combined and assessed between the resulting two eras. This also held ($p > 0.05$) when the two non-adrenal sites were combined and analyzed as one group.

The effects of the side of onset on survival was assessed in 233 cases. The survival of right side onset was a little better than that of left side onset with the 4-year survival rate of 54.8% ± 6.9% (56 cases) on the right and 51.7% ± 5.7% (77 cases) on the left side ($p > 0.05$).

TABLE IV. Distribution by Age at Diagnosis and Stage

Stage	I, II, IVs	III	IV	Total
AG 0E	37 (66.1)	9 (16.1)	10 (17.9)	56
AG 1<=E	16 (16.5)	24 (24.7)	57 (58.8)	97
	53 (34.6)	33 (21.6)	67 (43.8)	153

The figures in parentheses are row percentages.

TABLE V. Distribution by Age at Diagnosis and Site of Onset

Site	Non-adrenal	Adrenal	Total
AG 0E	23 (39.7)	35 (60.3)	58
AG 1<=E	27 (27.6)	71 (72.4)	98
Total	50 (32.1)	106 (67.9)	156

The figures in parentheses are row percentages.

Histological Subtype

In survival analysis 129 cases were neuroblastoma and 30 cases were ganglioneuroblastoma. Survival by these subtypes was assessed. Ganglioneuroblastoma patients had better outcomes than neuroblastoma patients ($p < 0.05$) with the 4-year survival rate of 72.1% ± 8.4% and 48.9% ± 4.5% respectively. Improvement in survival was steady in neuroblastoma patients ($p < 0.01$) with the 4-year survival rate of 38.5% ± 5.5% (79 cases) in the first era, 52.0% ± 10.0% (25 cases) in the second era, and 79.4% ± 8.2% (25 cases) in the third era. In ganglioneuroblastoma patients the 4-year survival rate improved from 60.0% ± 12.7% (15 cases) in the first era to 87.5% ± 11.7% (8 cases) in the second and 83.3% ± 15.2% (7 cases) in the third era. But this change was not statistically significant ($p > 0.05$). This may be partly due to the small number of cases.

Association Among Risk Factors

The risk factors analyzed above were related to each other. Therefore, associations among the risk factors were assessed after combining patients, in each factor, with similar survival outcomes. The resultant classifications for the risk factors were the following in the order of survival outcome: age at diagnosis (below 1 year, 1 year or more); stage (I or II or IVs, III, IV); site of onset (neck or thorax or abdominal or pelvic regions as non-adrenal site, adrenal gland); side (right, left); subtype (ganglioneuroblastoma, neuroblastoma); sex (male, female).

The association between age at diagnosis and the clinical stage is presented in Table IV. The majority of patients under 1 year of age with a favorable prognosis clustered in stage I, II, and IVs with a good prognosis. On the other hand the majority of patients 1 or more years with an unfavorable prognosis clustered in stage IV with a poor prognosis. The association assessed by the chi-square test was statistically significant ($p < 0.001$).

The association between age at diagnosis and site of onset is presented in Table V. While 60.3% of the patients below 1 year of age were in the adrenal gland group with an unfavorable prognosis, among the patients 1 or more years 72.4% were in the adrenal gland group. The association was statistically significant ($p < 0.05$).

The association between the clinical stage and site of onset is presented in Table VI. Nearly half of non-adrenal onset patients with a favorable prognosis belonged to the stage group of I, II, and IVs with a good prognosis, whereas nearly half of adrenal onset patients belonged to Stage IV with a poor prognosis. The association was statistically significant ($p < 0.05$).

Other associations among the risk factors were also assessed. An association between age at diagnosis and subtype became statistically significant ($p < 0.05$). Among the 58 patients under 1 year of age 3 patients (5.2%) were ganglioneuroblastoma with a favorable prognosis, whereas among the 101 patients above 1 or more years with a poor prognosis 27 patients (26.7%) were ganglioneuroblastoma ($p < 0.01$). The association was inverse in terms of prognosis. As for the association between site of onset and subtype, it was not statistically significant ($0.05 < p < 0.06$). Among the 50 patients of non-adrenal primaries with a favorable prognosis, 14 patients (28.0%) were ganglioneuroblastoma, whereas among the 106 patients of adrenal primaries with an unfavorable prognosis 16 patients (15.1%) were ganglioneuroblastoma. All the other 10 associations between risk factors were statistically non-significant ($p > 0.05$).

Multivariate Analysis for Risk Factors

As shown above, some risk factors showed close associations. Therefore, the Cox proportional hazards regression analysis was done to explore independent risk factors. Risk factors used in this analysis were those which yielded a significant difference in survival: age at diagnosis, histological subtype, stage, site of onset, and year of diagnosis. These factors were re-classified according to the survival outcomes; groups of patients who showed similar survival rates were combined in each factor. The resultant classifications became the following. Age at diagnosis: below 1 year of age; 1 or more years of age. Histological subtype: ganglioneuroblastoma; neuroblastoma. Stage: stage I, II, IVs; stage III;

TABLE VI. Distribution by Site of Onset and Clinical Stage

Stage		I, II, IVs	III	IV	Total
SITE	Non-adrenal	22 (47.8)	12 (26.1)	12 (26.1)	46
	Adrenal	31 (29.8)	21 (20.2)	52 (50.0)	104
		53 (35.3)	33 (22.0)	64 (42.7)	150

The figures in parentheses are row percentages.

TABLE VII. Independent Risk Factors in Neuroblastoma

Risk factor	Classification	Risk ratio	95%CI[a]
Age at diagnosis	<1/≥1	3.8	1.8–8.1
Stage	I, II, IVs/III/IV	2.5	1.6–3.7
Subtype	Ganglioneuroblastoma/ Neuroblastoma	2.2	1.1–4.6
Treatment era	1965–81/1982–86/1987–94	1.9	1.3–2.7
Site	Non-adrenal/Adrenal	1.8	1.0–3.4

[a]CI: Confidence interval

stage IV. Site of onset: non-adrenal (neck, thorax, abdominal, and pelvic region) region; adrenal gland. Year of diagnosis: 1965–1981; 1982–1986; 1987–1994. Excluding 9 cases with a missing information, 150 cases were available for this analysis.

The results obtained by the stepwise procedure are shown in Table VII. All the risk factors except for the site of onset became statistically significant independent risk factors ($p < 0.05$). The p-value for the site of onset was slightly above 0.05. The test for proportionality in hazards ratio were not significant ($p > 0.05$) except for age at diagnosis. The survival curve for age at diagnosis less than 1 year, shown in Figure 2, became flat after 16 months, whereas that for age at diagnosis above 2 years continued to decline. This accounts for the non-proportionality in the hazards ratio.

The following were derived from these results. Age at diagnosis was the most influential risk factor on survival, followed by the clinical stage, histological subtype, and treatment eras. The site of onset was a strong candidate for an independent risk factor coming next.

DISCUSSION

The survival of patients with neuroblastoma in this institution was improved during the past three decades. However, age at diagnosis, the clinical stage, the site of onset, and the histological type still remained as independent risk factors. Age above 12 months, Stage IV in the Evans classification, adrenal onset, and neuroblastoma rather than ganglioneuroblastoma were factors for poor prognosis. The progress in treatment strategies has not been substantial to overcome these prognostic factors.

Some statistical questions need to be stated here. As seen in the figures in the results, the survival curves tended to be flat after certain years. This tendency manifested earlier in good prognostic risk groups than in poor prognostic risk groups in respective figures presented in the results section. Therefore, the proportionality of hazards, which was assumed in the Cox regression analysis, was examined. Except for age at diagnosis, this assumption was not negated. To be certain that age at diagnosis would stand as an independent risk factor, the logistic regression analysis was carried out by the LOGISTIC procedure [21]. The outcome (as dependent) variable was tumor death. The use of this analysis may be justified for a small number of censored cases until 4 years after diagnosis. Risk factors were categorized in the same way as in the Cox regression analysis. Risk ratios yielded with a significance level at $p < 0.05$ were the following: 4.6 for age at diagnosis; 4.4 for the clinical stage; 3.2 for the treatment era; 3.1 for the site of onset. These risk ratios were a little larger than those obtained by the Cox regression analysis. Sex and the histological subtype were not independent risk factors by the stepwise procedure. In this analysis also age at diagnosis became the strongest risk factor.

Generally speaking, the results in this study agree with those in the past studies. Jaffe, in his extensive review article [11], raised the following as important risk factors for higher mortality: age at diagnosis not less than 1 year, the advanced stage except for IV-S and the primary site at the adrenal gland. He raised male patients and undifferentiated histology as possible risk factors for higher mortality. In this review article few studies employed a multivariate analysis. One of the few such studies was the study by Breslow and McCann [15] in which age and Evans stage were used and analyzed by the logistic regression analysis. Both factors remained as independent risk factors.

In a more recent report by Coldman et al. [16] age at diagnosis less than 1 year, advanced stages by Evans classification and a non-adrenal site were claimed to be independent risk factors by the logistic regression analysis. Sex of the patient was not an independent risk factor. In that study neither the order of significance nor the risk ratios of these factors were provided. Thomas et al. [17] reported, from the results of the logistic regression analysis, that in order of significance, stage, histology (neuroblastoma vs. ganglioneuroblastoma), and age at diagnosis were independent prognostic variables, and sex of the patient, nodal status at diagnosis, and individual treatment modalities were not significant prognostic variables. The risk ratios of these variables were not provided. Bowman et al. [9] identified, in order of significance, limited-disease stage by the Pediatric Oncology Group criteria, age less than 1 year, and non-adrenal primary site as independent predictors of a more favor-

able outcome through the Cox proportional hazards analysis. They also identified treatment era as an independent predictor and concluded that intensified therapy after 1979 substantially improved the survival. In their study relative risks for the risk factors were provided.

In addition to the above clinical factors recent studies raised laboratory and biological prognostic factors. In studies of un-selected patients raised were N-myc amplification [24], HER-2/neu and p53 [14], TRK protooncogene [25], and serum ferritin [26]. In studies of non-advanced patients raised were high levels of lactate dehydrogenase [27]. In studies of advanced patients raised were high levels of lactate dehydrogenase and low urinary excretion of vanillyl mandelic acid [28], leukopenia [29], and N-myc amplification [30]. In studies of thoracic vs non-thoracic neuroblastoma—the former site was a favorable factor—N-myc amplification, a high lactic dehydrogenase level and a low DNA index were poor prognostic factors [31]. Other laboratory risk factors claimed were the loss of heterozygosity on the short arm of chromosome 1 [32], neuron specific enolase activity [33], homogenously staining region [34], double-minute chromatin bodies [35], Ha-ras p21 expression [36], and apoptosis-supressing protein bcl-2 [37]. Laboratory and biological factors described above were not included in this study, as these factors were relatively recent claimed ones and their information was lacking in most cases used in this study. The magnitude and usefulness of these factors in identifying high risk patients need to be investigated.

As for the improvement in survival by year of diagnosis or treatment era, our results are comparable to or slightly better than those in other studies. In most studies including ours, survival curves were almost flat after 4 years, so the difference between 5-year and 10-year survival should be very little. In a study in Britain [38] the overall 5-year survival rate increased from 15% in the years 1971–73 to 43% in the years 1983–85; lower than ours. The 5-year survival rate in patients less than 1 year of age increased from 30% in the years 1971–73 to 77% in the years 1983–85; again lower than ours for the corresponding years. The improvement in survival rate in patients of 1 or more years was also unfavorable in their results. In another study in England [6], the 10-year survival rate in the years 1978–88 among patients less than 1 year of age was 87%; a little better than our results. But among patients of 1 or more years the survival rate was 8.5%; much lower than ours. In a study in Canada [39] the overall 10-year survival rate in the years 1977–86 was 55%, comparable to ours. The survival rates by Evans stage were also similar to ours. The survival in a hospital-based study in Denmark [40] seemed a little lower than ours. The 10-year survival rate in the years 1971–80 was 32%. The survival rate among patients less than 1 year of age, or that among Stage IV patients was also lower than ours. In a hospital-based study in the U.S.A [9], the 4-year survival improved from 34% in the years 1963–78 to 57% in the years 1979–88. The improvement in our study for the corresponding eras was from 45% to 52%. Our improvement was slightly smaller with a higher survival rate in the former era and a lower survival rate in the latter era.

The comparisons mentioned above, however, should be interpreted carefully. In a comparison of overall survival rates, differences in the composition of patients regarding the distribution of important prognostic factors such as age at diagnosis, stage, and site of onset could produce apparent differences in survival. Stratification by only one of these factors would not secure solid comparisons. Stratification by all of such factors would result in too few cases in each stratum. Use of some standardization methods or multivariate analysis techniques may be necessary for strict comparisons. Differences in the composition may come from selection bias. Hospital-based studies are vulnerable to this bias. In this connection it needs to be stated that the patients in this study were not likely biased towards better prognosis before 1983. The hospital served as the oldest and largest children's hospital to which patients with serious diseases were referred. Selection bias towards poor prognosis may have been entered. However, after 1983 the study patients included patients found by mass screening who were reported to be of good prognosis [41]. The 4-year survival rates after excluding these patients for the 3 treatment eras were the following: 42.0% for 1965–81, 58.1% for 1982–86, and 71.1% for 1987–94. The survival rate decreased by 2.5 points in 1982–86 and by 9.1 points in 1987–94.

The results of this study showed that in neuroblastoma the classical prognostic factors still overwhelmed the progress in the treatment. Further efforts to identify other risk factors, particularly laboratory ones, will be useful in the management of patients. To reduce mortality further in neuroblastoma, new treatment strategies coupled with identifying risk factors need to be developed. The tentative results of the controlled field studies seeking for the efficacy of mass screening are not necessarily promising [42]. A new strategy in mass screening also seems to be required.

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